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2019-04

Finne , P , Groop , P-H , Arffman , M , Kervinen , M , Helve , J , Gronhagen-Riska , C & Sund , R 2019 , ' Cumulative Risk of End-Stage Renal Disease Among Patients With Type 2 Diabetes : A Nationwide Inception Cohort Study ' , Diabetes Care , vol. 42 , no. 4 , pp. 539-544 . https://doi.org/10.2337/dc18-1485

http://hdl.handle.net/10138/313693
https://doi.org/10.2337/dc18-1485

unspecified
publishedVersion

Cumulative Risk of End-Stage Renal Disease Among Patients With Type 2 Diabetes: A Nationwide Inception Cohort Study

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Diabetes Care 2019;42:539–544 | https://doi.org/10.2337/dc18-1485

OBJECTIVE

To estimate long-term cumulative risk of end-stage renal disease (ESRD) after diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

This nationwide population-based inception cohort study included 421,429 patients with type 2 diabetes diagnosed in 1990–2011; patients were followed until the end of 2013. Data linkage between several national health care registers in Finland, covering 100% of the population, enabled the inclusion of almost all inhabitants who started taking diabetes medication or were hospitalized for diabetes. Cumulative risk of ESRD and hazard ratios [HR] for ESRD and death were estimated according to age, sex, and time period of diabetes diagnosis.

RESULTS

Among 421,429 patients with type 2 diabetes, 1,516 developed ESRD and 150,524 died during 3,458,797 patient-years of follow-up. Cumulative risk of ESRD was 0.29% at 10 years and 0.74% at 20 years from diagnosis of diabetes. Risk was higher among men than among women (HR 1.93 [95% CI 1.72–2.16]), decreased with older age at diagnosis (HR 0.70 [95% CI 0.60–0.81] for age 60–69 vs. 40–49 years), and was lower for those diagnosed in 2000–2011 than in 1990–1994 (HR 0.72 [95% CI 0.63–0.81]). Patients diagnosed with diabetes in 2000–2011 had lower risk of death during follow-up than those diagnosed in 1990–1994 (HR 0.64 [95% CI 0.63–0.65]).

CONCLUSIONS

Cumulative risk of ESRD is minimal among patients with type 2 diabetes compared with their risk of death. Patients diagnosed with diabetes at an older age have a lower risk of ESRD due to higher competing mortality.

Diabetes is a major noncommunicable disease with an estimated global prevalence of 9% in 2014 (1). The number of adults with diabetes worldwide is expected to increase from 387 million in 2014 to 592 million in 2035, with most having type 2 diabetes (2,3). One of the most devastating complications of diabetes is chronic kidney disease. Relative to the general population, persons with diabetes have a 5- to 13-fold risk of end-stage renal disease (ESRD) (4–6). ESRD extensively increases risk of death among patients with diabetes (7–9), and diabetes is the most common cause of ESRD in most

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Received 11 July 2018 and accepted 1 January 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1485/-/DC1.

industrialized countries (10); a study of 18 European countries showed that type 2 diabetes was the most frequent renal disease leading to initiation of renal replacement therapy (11).

Most earlier studies of the incidence of ESRD in diabetes have used prevalence cohorts, which means that patients have not been followed since their diabetes diagnosis. Patients with all types of diabetes typically have been included, and the incidence rate of ESRD has been 1–9 per 1,000 patient-years (4,12–14), with larger estimates among African Americans and those with a longer duration of diabetes. Notably, a prevalence cohort study from Italy including only patients with type 2 diabetes showed that only 10 of 1,408 patients developed ESRD over a 10-year follow-up (15). To our knowledge, only two inception cohort studies have addressed the incidence of ESRD. The UK Prospective Diabetes Study followed 5,097 patients with newly diagnosed type 2 diabetes, only 14 of whom required renal replacement therapy during the median follow-up of 10.4 years (16). However, the cumulative risk was not computed, and any subgroup analyses would not have been possible because of the small number of patients who developed ESRD. A population-based study from Saskatchewan, Canada, included 90,429 incident cases of diabetes among the adult study population, and the results showed an almost threefold risk of ESRD among indigenous patients (17). Among nonindigenous patients, the cumulative incidence of ESRD was ~1–2% at 20 years since the diabetes diagnosis.

We and others have estimated the cumulative risk of ESRD in inception cohorts of patients with type 1 diabetes (18–21). Although type 2 diabetes is a major cause of ESRD, cumulative risk of ESRD after type 2 diabetes has been diagnosed is not well known. Here, we present the cumulative risk of ESRD during a 24-year follow-up of a nationwide population-based cohort of 421,429 patients newly diagnosed with type 2 diabetes in 1990–2011.

RESEARCH DESIGN AND METHODS

Study Population

Patients with type 2 diabetes were identified from the Diabetes in Finland (FinDM) database (22), which is a research register created through cooperation between the Finnish National Institute of Health and Welfare, the Social Insurance Institution of Finland, and the Finnish Diabetes Association. The FinDM register was established by using data from several national health care databases such as the Hospital Discharge Register (1969–1993), the Finnish Health Care Register (1994–2011), the Hospital Benchmarking database (1998–2011), and the Medical Birth Register (1987–2011). The Social Insurance Institution of Finland provided information on patients entitled to reimbursement for diabetes medication (1964–2011) and purchases of prescribed antidiabetes drugs (1993–2011). Among the patients in the FinDM database, most (93%) were identified by the use of antidiabetes medication; 58% were identified on the basis of their use of services taken from the Hospital Discharge Register, the Finnish Health Care Register, or the Hospital Benchmarking database. Of these patients, 41% were identified only on the basis of medication; 7%, on the basis of services; and 52%, on the basis of both medication and services. Almost all Finnish inhabitants who started taking antidiabetes medication or were hospitalized for diabetes were included in the FinDM database, whereas persons who had diabetes but were not taking antidiabetes medication or never received hospital treatment were not included. The date of diabetes diagnosis was defined as the first registration of diabetes in any of the four aforementioned registers. Patient inclusion in the FinDM database has been evaluated through the use of external data sources (23).

We created a definition of type of diabetes that was primarily based on medicine purchases; it has been described in detail elsewhere (22). Patients who receive continuous insulin treatment but have never taken any oral antidiabetes medication were defined as having type 1 diabetes, whereas all others were considered as having type 2 diabetes. The diagnosis provided by hospital providers was also used in the definition. To ensure that we included only patients with type 2 diabetes, we excluded patients with diabetes who were younger than 40 years old when their diabetes diagnosis was registered. Data were available for 609,453 patients with type 2 diabetes first entered in the database between 1972 and 2011. As initiation of dialysis among patients with type 2 diabetes and elderly patients was less frequent in the 1970s and 1980s, we decided to analyze the cumulative risk of ESRD only in patients diagnosed with type 2 diabetes in more recent years—between 1990 and 2011 (n = 422,224). Patients were excluded if they had ESRD when type 2 diabetes was diagnosed (n = 795). Thus the final inception cohort included 421,429 patients aged 40 years or older. Notably, during the same time period, 7,451 patients aged 20–29 years and 14,970 patients aged 30–39 years were diagnosed with diabetes according to the same criteria, but they were not included in this study. When presenting the incidence rate of ESRD according to the time period in which ESRD occurred, patient-years for all patients with type 2 diabetes contributing patient-years in 1990–2011 were included in the denominator, as were patients diagnosed with diabetes before 1990 who were not included in the inception cohort.

Data on initiation of renal replacement therapy were retrieved from the Finnish Registry for Kidney Diseases, which covers an estimated 97–99% of all patients who have received chronic dialysis and kidney transplantation since 1964 (24). ESRD was defined as receipt of renal replacement therapy. The FinDM database was linked to the Finnish Registry for Kidney Diseases until 31 December 2013 by using individual personal identity codes, which are used in all administrative registers in Finland. Data on deaths were retrieved from the Causes of Death Register of Statistics Finland (1971–2013). The FinDM Study was approved by the Ethics Committee of the National Institute for Health and Welfare, Helsinki, Finland, on 23 January 2014.

Statistical Analysis

Patients with type 2 diabetes were followed from their first entry in the FinDM database until ESRD or death occurred, or until follow-up ended on 31 December 2013. When calculating the cumulative risk of ESRD, we accounted for death as a competing risk event. Hazard ratios (HR) of ESRD according to age group, sex, and time period when type 2 diabetes was diagnosed were modeled by using proportional subdistribution hazards regression, which considered death as a competing risk event (25). When calculating risk of death, follow-up did not end when ESRD occurred. Cumulative risk

of death was estimated by using Kaplan-Meier curves. Cox proportional hazards regression models were fitted to provide HR of death associated with age group, sex, time of diabetes diagnosis, and time-dependent occurrence of ESRD. All first-degree interactions between explanatory variables were tested. Incidence was calulated by dividing the number of patients with ESRD by person-time at risk.

We used R statistical software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) with the cmprsk package to calculate cumulative incidence (i.e., cumulative risk) of ESRD (cuminc function) and to perform proportional subdistribution hazards regression (crr function). All other analyses were conducted in SAS version 9.3 (SAS Institute Inc.).

RESULTS

Of 421,429 patients diagnosed with type 2 diabetes in 1990–2011, 1,516 developed ESRD and 150,524 died before the end of 2013. The total number of patient-years of type 2 diabetes was 3,458,797 (Table 1). The median follow-up was 6.82 years. A sex difference was found for age distribution: 70% of women and 55% of men were 60 years or older when type 2 diabetes was diagnosed.

The cumulative risk of ESRD was 0.29% at 10 years and 0.74% at 20 years since the diagnosis of type 2 diabetes. The risk was higher among men, but in both sexes it decreased with increasing age (Fig. 1).

Figure 2 shows the incidence rate of ESRD among patients diagnosed with type 2 diabetes between 1990 and 2011. The incidence rate increased with longer duration of diabetes and was the highest among those diagnosed with diabetes during the earliest period, 1990–1994.

The proportional subdistribution hazards regression model showed decreasing HR for ESRD with increasing age (Table 2). Men had a 93% higher risk of ESRD than women. The risk of ESRD was lower for those diagnosed with diabetes during a later time period. No statistically significant first-degree interactions were detected between the variables age, sex, and period during which type 2 diabetes was diagnosed.

As an alternative analysis, the incidence rate of ESRD was calculated among all prevalent cases of type 2 diabetes in the time periods 1990–1999 and 2000–2011, thus including patients who were diagnosed with type 2 diabetes before 1990 but who contributed patient-years in 1990–2013 (Supplementary Fig. 1). During a total of 4,345,251 patient-years, 2,127 patients developed ESRD, resulting in an incidence rate of 0.49 per 1,000 patient-years (95% CI 0.47–0.51). The incidence rate was higher among men (0.66 [95% CI 0.63–0.70]) than among women (0.33 [95% CI 0.31–0.35]) and in 2000–2013 (0.53 [95% CI 0.51–0.56]) than in 1990–1999 (0.37 [95% CI 0.34–0.41]). The incidence rate of ESRD had increased most among men older than 70 years. For both men and women, the incidence rate of ESRD peaked among those aged 60–79 years.

Among patients diagnosed with type 2 diabetes between 1990 and 2011, the cumulative risk of death was 34% at 10 years and 64% at 20 years since the diagnosis of diabetes. The HR of death increased with increasing age (Table 2). Patients aged 70–79 years when diabetes was diagnosed had an eightfold risk of death during the follow-up compared with those aged 40–49 years. When calculating HR for death, occurrence of ESRD was included in the multivariable model as a time-dependent variable (not shown in Table 2), and ESRD increased the risk of death 4.2-fold during follow-up. Excluding the time-dependent variable ESRD caused marginal changes in the model parameters. In the interaction analysis, sex modified the effects of age and ESRD on HR for death. Among men, ESRD increased risk of death 3.8-fold and among women, 5.6-fold. Age (70–79 vs. 40–49 years) showed an HR for death of 7.4 among men and 9.8 among women. Also, a statistically significant interaction occurred between age and ESRD during follow-up, showing a weaker association between ESRD and risk of death among those aged 70 years or older (HR 3) than among those younger than 60 years (HR 5).

Table 1—Number of patients diagnosed with type 2 diabetes in 1990–2011 and numbers of patient-years, ESRD cases, and deaths until the end of 2013 according to age and sex

Age-group (years), by sex	Patients with type 2 diabetes	Patient-years	ESRD cases	Deaths
40–49				
Males	31,465	317,663	239	5,100
Females	18,520	192,669	73	1,695
Total	49,985	510,332	312	6,795
50–59				
Males	64,502	586,784	356	13,368
Females	43,583	434,523	142	5,618
Total	108,085	1,021,307	498	18,986
60–69				
Males	63,926	498,862	297	21,916
Females	56,965	545,698	165	15,790
Total	120,891	1,044,560	462	37,706
70–79				
Males	40,272	249,330	133	22,503
Females	56,734	433,455	93	29,804
Total	97,006	682,785	226	52,307
≥80				
Males	13,145	51,605	11	10,085
Females	32,317	148,208	7	24,645
Total	45,462	199,813	18	34,730
All ≥40				
Males	213,310	1,704,244	1,036	72,972
Females	208,119	1,754,553	480	77,552
Total	421,429	3,458,797	1,516	150,524

CONCLUSIONS

This large, nationwide inception cohort study shows that the risk of ESRD is low—only 0.74% at 20 years from the diagnosis of diabetes—among more than 420,000 patients with type 2 diabetes who were followed for up to 24 years. During the follow-up (~3.5 million patient-years), only 1,516 patients

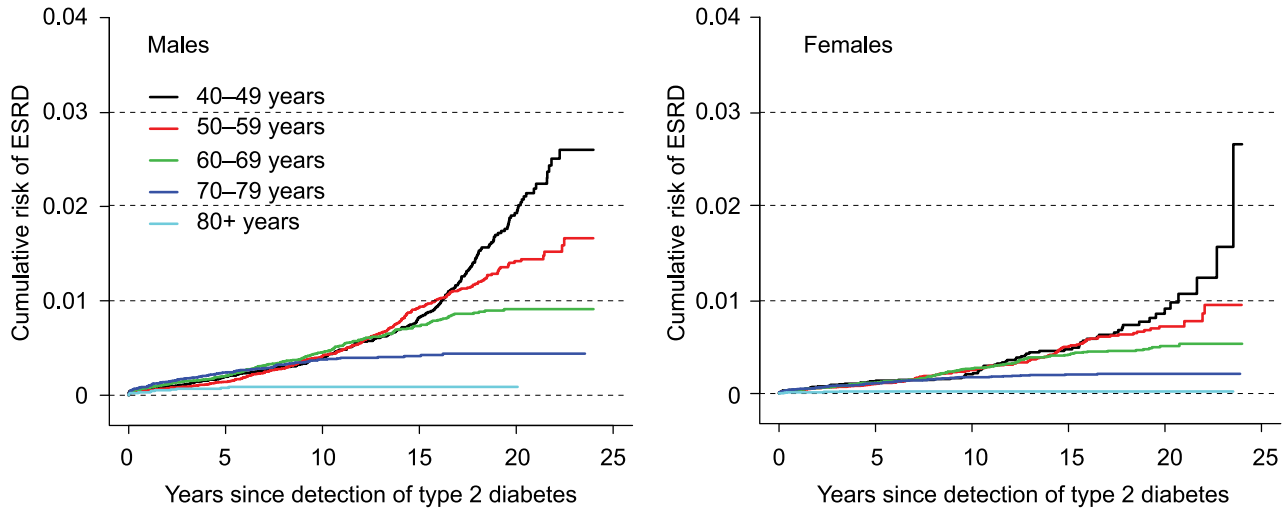

Figure 1—Cumulative risk of ESRD, by age-group, among male and female patients with type 2 diabetes detected in 1990–2011.

developed ESRD, while more than 150,000 died. The number of deaths was 100-fold higher than the number of ESRD cases. Thus death was a main competing risk event, and it was accentuated in the older age groups. The cumulative risk of ESRD was highest among those diagnosed with diabetes at the youngest age, 40–49 years; risk decreased continuously while mortality increased among the older age groups. By contrast, the incidence rate of ESRD was highest among patients aged 60–79 years, which reflects the typical age at which ESRD occurs among people with type 2 diabetes. Male patients had a twofold risk of ESRD; this male predominance is a common finding for all causes of ESRD (10).

The study also shows that cumulative risk of ESRD was smaller in recent years than at the beginning of the 1990s. By contrast, the incidence rate of ESRD has increased among all prevalent cases of type 2 diabetes, which demonstrates that the nature of the incidence rate is different from that of cumulative risk. This may be explained by longer diabetes duration of the patients considered in the 2000–2013 period. We show that the incidence rate of ESRD increases with duration of diabetes, which was also observed earlier (12). Our finding of a decrease in patients' cumulative mortality reflects improved diabetes care.

Our study has several strengths. The study population is based on a comprehensive linkage of data from multiple national health care registers, providing complete coverage of the Finnish population. All people with type 2 diabetes in Finland were included from when antidiabetes medication was initiated; that is, this inception cohort included a clearly specified starting point for follow-up. Data on death were also retrieved from a complete national database. Data on renal replacement therapy were estimated to be 97–99% complete. Our study is unique in that it is, to our knowledge, the only nationwide and by far the largest inception cohort study of the risk of ESRD among people with type 2 diabetes. This enables a much more accurate estimation of the cumulative risk of ESRD than is available from earlier studies.

Some limitations of the study warrant discussion. We did not have information on earlier stages of chronic kidney disease, such as albuminuria or elevated creatinine, but this did not affect the estimates of cumulative risk of ESRD. We also lacked information on clinical parameters such as HbA_{1c}, blood pressure, or dyslipidemia. Our study did not include patients with diabetes who received only dietary treatment, nor did it include people with undiagnosed diabetes. Two large, population-based health surveys were performed in Finland in 2000 and 2011, and they showed that 25–30% of respondents with self-reported diabetes received only dietary treatment (26). In a cross-sectional study, the glucose tolerance test was performed in 2004 on randomly selected Finnish inhabitants aged 45–74 years (27). Results showed that 16% of men and 11% of women had diabetes, and in only less than half of those people had diabetes been diagnosed before. Thus, it is clear

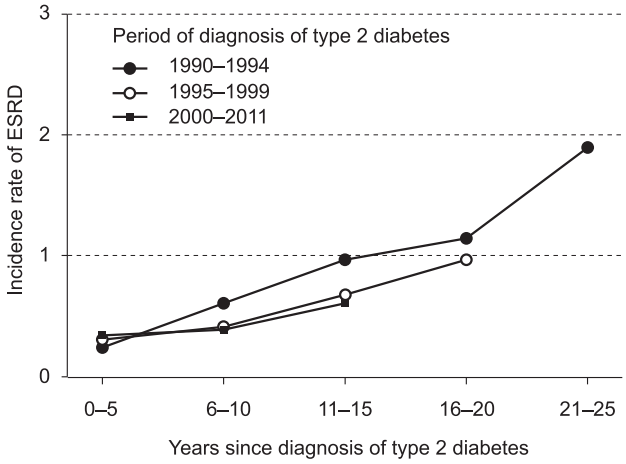

Figure 2—Incidence rate of ESRD per 1,000 patient-years, by period during which type 2 diabetes was diagnosed and by the duration of type 2 diabetes in the inception cohort.

Table 2—HR of ESRD and death among patients diagnosed with type 2 diabetes in 1990–2011 and numbers of patient-years, ESRD cases, and deaths until the end of 2013 according to age-group and sex

	Patients with type 2 diabetes	Patient-years	ESRD cases	Deaths	HR (95% CI)	
					ESRD	Death
Age at diabetes diagnosis (years)						
40–49	49,985	510,332	312	6,795	1	1
50–59	108,085	1,021,307	498	18,986	0.82 (0.71–0.94)	1.6 (1.5–1.6)
60–69	120,891	1,044,560	462	37,706	0.70 (0.60–0.81)	3.2 (3.2–3.3)
70–79	97,006	682,785	226	52,307	0.45 (0.37–0.54)	8.3 (8.0–8.5)
≥80	45,462	199,813	18	34,730	0.09 (0.05–0.14)	22.8 (22.2–23.4)
Sex						
Female	208,119	1,754,553	480	77,552	1	1
Male	213,310	1,704,244	1,036	72,972	1.93 (1.72–2.16)	1.5 (1.5–1.6)
Period when type 2 diabetes was diagnosed						
1990–1994	69,514	845,281	508	50,464	1	1
1995–1999	75,193	878,826	387	40,722	0.77 (0.67–0.88)	0.82 (0.81–0.83)
2000–2011	276,722	1,734,690	621	59,338	0.72 (0.63–0.81)	0.64 (0.63–0.65)

that our study merely includes a selection from among all patients with type 2 diabetes, as a considerable proportion of people with diabetes remain undiagnosed. However, this is also the case in other population-based studies, because nearly half of all diabetes cases globally are estimated to be undiagnosed (28). We defined ESRD as receipt of renal replacement therapy, but not all patients with ESRD receive dialysis therapy or a renal transplant. At Helsinki University Hospital, all decisions to initiate renal replacement therapy have been registered since the 1990s. In ~20% of patients with ESRD, renal replacement therapy was not initiated (E. Honkanen, A. Esktrand, personal communication). In the 1970s and 1980s, renal replacement therapy was hardly ever initiated for patients with type 2 diabetes, but the number of these patients entering dialysis annually increased sharply through the 1990s until 2000, after which the rate has remained relatively unchanged (24). It should also be noted that the annual number of people diagnosed with type 2 diabetes increased during the study period, probably as a consequence of increased screening for type 2 diabetes, which leads to earlier detection or detection of cases that previously would have remained undetected. We assume that earlier detection of diabetes is connected to lower cumulative risk of complications. For this reason, cumulative risk of ESRD between time periods of diabetes diagnosis should be compared carefully.

Most earlier studies of ESRD risk in patients with diabetes were based on prevalence cohorts (4,12–15), which means that, contrary to inception cohort studies, patients were not included in the study at any specified point in the early course of diabetes (e.g., at time of diagnosis) and that the period since diabetes was detected varied. The overall incidence rate of ESRD has varied between 1 and 9 per 1,000 patient-years. In Caucasians, the incidence rate of ESRD is lower: between 1 and 4 per 1,000 patient-years (13,15), which is still higher than the incidence rate of 0.49 per 1,000 patient-years reported here. The difference may be explained by the relatively low overall incidence of renal replacement therapy in Finland (10). Notably, in the UK Prospective Diabetes Study, 14 of 5,097 patients (0.3%) with type 2 diabetes developed ESRD, which is similar to the cumulative risk of 0.29% at 10 years in our study (16).

Patients' risk of developing ESRD after type 2 diabetes has been diagnosed can be reliably estimated only by calculating the cumulative incidence of ESRD in large inception cohort studies. To our knowledge, only one such study has been published. Jiang et al. (17) compared the cumulative incidence of ESRD between indigenous and nonindigenous patients diagnosed with diabetes in the Canadian province of Saskatchewan. Among nonindigenous persons, the risk of ESRD—less than 1% at 10 years and 1–2% at 20 years since diagnosis of diabetes—was comparable to our findings. Patients aged 60 years or older when diabetes was diagnosed had a lower cumulative risk of ESRD due to higher competing mortality, which also was the case in our study. The similarity of our findings in northern Europe with those from Canada supports the generalizability of our results to other highly developed countries.

Our study shows that risk of ESRD is small among people with type 2 diabetes. This may seem unexpected, because a substantial proportion of patients are entering early stages of chronic kidney disease, with 25% of patients having microalbuminuria and 5% having macroalbuminuria 10 years after their diabetes diagnosis (16). These early stages of kidney disease are associated with increased premature mortality; this contributes to the fact that relatively few patients develop ESRD, as death is a common competing risk event. However, diabetes is the most common cause of ESRD in most industrialized countries, and because of a high and increasing prevalence of diabetes among the general population, a considerable absolute number of patients with type 2 diabetes need dialysis therapy (10,11). Our findings are important for clinicians who inform patients with type 2 diabetes about the associated risks and complications. As type 2 diabetes is a common disease, our study also has implications for policy makers. Notably, people diagnosed with type 2 diabetes at an older age have a lower risk of ESRD and a higher risk of death than those diagnosed at a younger age. The cumulative risk of ESRD and death has decreased since the early 1990s among people with type 2 diabetes. This may be the result of improvements in

diabetes care, but it may also reflect the inclusion in our study cohort of people at an earlier stage of diabetes.

In conclusion, although type 2 diabetes is a major cause of ESRD, our study indicates that cumulative risk of ESRD in people with newly diagnosed type 2 diabetes is conspicuously low: only 0.74% at 20 years after diabetes was diagnosed. Moreover, the cumulative risk of ESRD decreases with older age at the time of diabetes diagnosis, mainly because of competing mortality. Future research should focus on how hypertension, hyperglycemia, dyslipidemia, and other treatable clinical factors affect the risk of people with type 2 diabetes developing ESRD.

Funding. This study was supported by grants from Medicinska Understödsföreningen Liv och Hälsa and Finska Läkaresällskapet and was partially funded by the Academy of Finland (project number 277939).

The funders had no role in study design; in collection, analysis, or interpretation of data; in writing this report; or in the decision to submit the article for publication.

Duality of Interest. P.-H.G. is a global advisory board member for and has received lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Co., Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi; is a global advisory board member for AbbVie Inc. and Janssen Pharmaceutica; and has received lecture fees from ELO Water. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.F. designed the study, collected and interpreted data, performed the literature search, and wrote the first draft of the manuscript. P.-H.G., M.K., J.H., and C.G.-R. interpreted data and wrote the manuscript. M.A. collected, interpreted, and analyzed the data and wrote the manuscript. R.S. designed the study; collected, analyzed, and interpreted the data; and wrote the manuscript. P.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented as a poster at the 55th ERA-EDTA Congress, Copenhagen, Denmark, 24–27 May 2018.

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